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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,824	10/23/2003	John Langenfeld	54704.8036.US03 RWJ-01-02	1322

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,824	LANGENFELD, JOHN	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14,16 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,14,16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20050926*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice of Non-Compliant Amendment.

DETAILED ACTION

1. The amendment filed September 1, 2005 is acknowledged and has been entered. Claims 1 and 16 have been amended.

2. Claims 1, 14, 16, and 18 are pending in the application and currently under prosecution.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

4. The information disclosure filed September 22, 2005 has been considered. An initialed copy is enclosed.

Response to Amendment

5. It is noted that the amendment filed September 1, 2005 is not compliant with the rules set forth under 37 C.F.R. § 1.121, since the listing of claims does not show each and every change that has been made to claim 16 relative to the preceding version. As explained on the attached Notice of Non-Compliant Amendment, the period punctuating claim 16 has been deleted and replaced by a comma but the claim is not marked appropriately to show this change.

Although the amendment is non-compliant, in the interest of advancing prosecution and in lieu of simply mailing the Notice of Non-Compliant Amendment, Applicant is reminded to adhere to the requirements set forth under 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003).

Briefly, the revised amendment practice now requires a listing of all claims beginning on a separate sheet. Each claim ever presented must be included in the listing of claims together with a single proper status identifier in parentheses. The permissible status identifiers include: "original", "currently amended", "canceled",

"withdrawn", "withdrawn-currently amended", "previously presented", "new", and "not entered". The text of all pending claims, including withdrawn claims, must be presented. Markings to show only the changes made in the current amendment relative to the immediate prior version should be included with the text of all currently amended claims, including withdrawn claims that are amended. Added text must be shown by underlining the added text. Generally deleted text must be shown by strikethrough (e.g., ~~strikethrough~~); or if the strikethrough cannot be easily perceived, and for deletion of five or fewer characters, the deleted text may be marked by the inclusion of deleted text in double brackets (e.g., [[444]]). The text of "canceled" and "not entered" claims must not be presented; and consecutive "canceled" or "not entered" claims may be grouped together in one line (e.g., Claims 1-11 (canceled); Claims 51-62 (not entered)).

Priority

6. Applicant has claimed benefit of the earlier filing date of copending U.S. Application No. 10/044,716, filed January 11, 2002, which, in turn, claims benefit of U.S. Provisional Application No. 60/261,252, filed January 12, 2001.

However, as explained in the preceding Office action, Applicant has not complied with one or more conditions for receiving the benefit of the earlier filing dates of the provisional application under 35 U.S.C. § 120 and therefore the effective filing date of the instant claims is considered to be the date that the present application was filed, namely October 23, 2003.

At pages 17 and 18 of the amendment filed September 1, 2005, Applicant has traversed this decision, arguing that it is a general principle of biology and pharmacology that if an agent has been shown to enhance a response, then inhibition of the agent's activity is a direct strategy for producing the opposite effect, which in this instance would be understood to be inhibition of vascularization.

Applicant's argument has been carefully considered but not found persuasive. The reasons that this application does not properly benefit from the earlier filing date of the copending U.S. Application No. 10/044,716 are set forth in the section 4 of the preceding Office action. In particular, there is no showing, prophetic or otherwise, that

the inhibition of an activity of BMP-2 reduces vascularization of a tumor. Furthermore, there is factual evidence of record that shows that BMP-4, rather than BMP-2, is overexpressed in the tumor cells that were used in the disclosed studies. Moreover, only the instant application describes an antibody that binds specifically to BMP-2 without cross-reacting to BMP-4, such that results described in the prior filed copending application cannot be taken as evidence that BMP-2, as opposed to BMP-4, is overexpressed in the cancer cell lines and lung cancer specimens tested.

Furthermore, as amended the claims are drawn to a method for reducing vascularization of a BMP-2-overexpressing tumor in a tumor comprising administering to a subject an inhibitor of BMP-2 activity that comprises noggin. Copending U.S. Application No. 10/044,716 does not provide an enabling disclosure of the claimed invention, since it does not teach the effect upon tumor vascularization of administering an inhibitor of BMP-2 activity, which comprises noggin. At paragraph [00142] the copending application describes an analysis that could be performed to assess the effects upon tumor growth and vascularization in mice by inoculating with lung cancer cells mice in the presence of agarose beads coated with albumin, BMP-2, or noggin, but it does not describe, or even prophesize reduced tumor vascularization in the presence of noggin. Moreover, this disclosure does not adequately describe the claimed invention, as it does not reasonably provide written support for reducing vascularization of a BMP-2-overexpressing tumor in a tumor comprising administering to a subject an inhibitor of BMP-2 activity that comprises noggin.

Again, to receive benefit of the earlier filing date under 35 USC § 120, the claims must be directed to an invention that is disclosed in the prior application; and that earlier disclosure must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. § 112. In this instance, for the reasons addressed herein, the description by the earlier filed application of the invention that is claimed in this application is not deemed sufficient to satisfy these requirements. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Grounds of Objection and Rejection Withdrawn

7. Unless specifically reiterated below, Applicant's amendment and/or arguments filed September 1, 2005 have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed April 27, 2005.

Grounds of Objection and Rejection Maintained

Specification

8. The objection to the specification, because the use of numerous improperly demarcated trademarks, is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although it appears that Applicant has made a bona fide attempt to resolve this issue by amending the specification to properly demarcate trademarks, there are still additional examples of improperly demarcated trademarks (e.g., GenBank™ (paragraph [00074]) and Tween™ (paragraph [00164])).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

9. The objection to the specification, as containing disclosures by the impermissible referral to embedded hyperlinks and/or other forms of browser-executable code, and to the Internet contents so identified, is maintained. Reference to hyperlinks and/or other forms of browser-executable code, and thus to the Internet contents so identified, *is impermissible and therefore requires deletion.*

At page 18 and 19 of the amendment filed September 1, 2005, Applicant has stated that references to such websites, and thus to their content, have been deleted from the disclosure.

Actually, Applicant while has amended the specification to delete "www.cancer.org" from the disclosure at page 86, it has been further amended to add the following: "(which can be found at the webpage index at the cancer.org website on the world wide web)". Thus, the disclosure still contains a reference to the website, and to the Internet contents so identified.

Again, the attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code, for example, (i.e., any reference to the contents of an Internet website) is considered to be an improper incorporation by reference and requires deletion.

By way of further explanation, MPEP 608.01(p) does not provide for incorporation of essential *or* non-essential material by reference to, for example, hyperlinks or other forms of browser-executable code. Essential subject matter may only be incorporated by reference to (1) US patents and pending US applications, or patents or other publications published by a foreign country or a regional patent office, (2) non-patent publications, (3) a US patent or application which itself incorporates material by reference, or (4) a foreign application. Non-essential information may be incorporated by reference to (1) patents or applications published by the United States, or patents or other publications published by a foreign country or a regional patent office, (2) prior filed, commonly owned US applications, (3) non-patent publications.

It is impermissible that a patent's disclosure incorporate essential or non-essential material by reference to, for example, embedded hyperlinks and/or other forms of browser-executable code, because the information contained in the websites or databases to which the hyperlinks or other forms of browser-executable code connect may not be maintained on the Internet for the duration of the patent's term and may not contain the same information after the filing date of an application that was contained in the website or database on or before the filing date of the application. Since the information contained in a website may vary, it is not evident that information contained

in a website will always remain useful the practitioner or even applicable to the invention; and information contained in an extinct website cannot possibly be helpful to the practitioner. Furthermore, the validity of a patent containing a reference to a hyperlink or other form of browser-executable code may be reasonably questioned if the website(s) to which the hyperlink(s) connect were relied upon by the patentee(s) to provide sufficient disclosure or description of the invention to meet the requirements of 35 USC § 112, first and second paragraphs. As such, recitation of such references is not permitted.

For additional clarity, a hyperlink or other form of browser-executable code may be permitted if the hyperlink or other form of browser-executable code is part of the claimed invention, but in such a case, the Office would disable the hyperlink or other form of browser-executable code.

In general, if the Applicant expects to rely upon the information contained in the websites or databases referred to by such disclosures to satisfy the requirements set forth under 35 U.S.C. § 112, first paragraph, or to provide antecedent basis for the subject matter of claims in the instant application or related applications, and if the material is properly incorporated by reference in the referencing application, Applicant would be required to amend the specification of the referencing application to include the material incorporated by reference to the hyperlink or other forms of browser-executable web, or other non-permissible sources and to provide a declaration by Applicant or Applicant's representative stating that the amendatory material consists of the same material incorporated by reference in this application. See MPEP § 608.01(p).

If Applicant intends that information contained at the websites to which the disclosures refer be incorporated, Applicant is required to amend the specification to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Rejections - 35 USC § 112

10. The rejection of claims 1, 14, 16, and 18 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At pages 20-23 of the amendment filed September 1, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Applicant has argued the claim amendments have resolved this issue in light of the experiments described at page 58 of the specification and the data presented in Figure 10.

Claims 1 and 14 are directed to a method for reducing vascularization of a BMP-2-overexpressing tumor in a subject comprising administering to a subject a therapeutically effective amount of a BMP-2 activity inhibitor comprising noggin, whereas the processes of claims 16 and 18 comprise administering to a subject a therapeutically effective amount of a nucleic acid molecule (i.e., a vector) encoding a BMP-2 activity inhibitor comprising noggin.

The specification teaches the claimed process provides a means for treating or preventing the development of a tumor in a patient diagnosed; see, e.g., the abstract and paragraph [00025].

Applicant has asserted that because the specification shows reduced tumor vascularization and growth in immunodeficient nude mouse model after co-injecting A549 human lung cancer cells and mouse noggin (i.e., the polypeptide of SEQ ID NO: 2), the skilled artisan could without undue or unreasonable experimentation clinically administer to a human patient diagnosed with a BMP-2-overexpressing tumor a therapeutically effective amount of an inhibitor of BMP-2 activity that comprises noggin and thereby reduce tumor vascularization and treat the cancer. However, the position of the Office is that such use of the claimed invention would not be reasonably enabled by the instant specification, as the skilled artisan could not do so without first establishing the role of BMP-2 in lung cancer, determine whether or not its inhibition would be clinically advantageous, and, if so, identifying and making a suitable inhibitor of BMP-2 activity that comprise noggin, such that tumor vascularization is reduced and the patient clinically benefits from the treatment.

As evidenced by Langenfeld et al. (2003) and Langenfeld et al (2004) (both of record) (i.e., the Applicant's own work published after the filing date sought by Applicant in the instant application), the amount of guidance, direction and exemplification is not sufficient to enable such use of the claimed invention. There are paradoxical, conflictive results reported in the literature, which indicate the role of BMP-2 in cancer is not well

enough understood to permit reasonable use of the claimed invention without first performing additional undue and unreasonable experimentation to establish its role and determine if inhibiting its activity will provide therapeutic benefit to patients diagnosed with cancer.

Addressing Applicant's assertion that the results of their studies, which were performed *in vivo,* outweigh the paradoxical and contrary results of others' studies performed using the same cell line but *in vitro*, it is noted that Gura (or record) and Bergers et al. (of record) address the common lack of extrapolation of the results of studies performed *in vivo* using mouse models to accurately and reliably predict the effects of the same treatments of human patients. As a consequence of such poor extrapolation, Gura teaches studies using mouse models often lead development of good mouse drugs rather than good human drugs, and Bergers et al. suggests careful evaluation of the effects of therapeutic agents in humans before transitioning from preclinical studies to clinical application.

Even so, Applicant has asserted that their use of human A549 mouse xenografts for evaluating the therapeutic efficacy of administering to a human an inhibitor of BMP-2 activity that comprises noggin humans should be sufficient to enable the skilled artisan to use the claimed invention. While such a model has been utilized to evaluate and predict the therapeutic efficacy of treating humans using experimental drugs, its use should not be considered sufficient to show that the claimed invention can be used without undue or unreasonable experimentation. Due to poor extrapolation of the results, their use to accurately and reliably predict the effectiveness of treating humans with the same agent or regimen is limited. Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that "[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract). Furthermore, Schuh discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1). Given the noted limitations of xenograft models,

Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer.* 2004 Apr; **40** (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotopic models have been developed; see entire document (e.g., the abstract). In such "orthotopic" models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

To contrast that disclosed in the instant application, the specification teaches that inoculating mice with A549 tumor cells in the presence of mouse noggin reduced the growth of tumors at that site in nude mice.

The position of the Office that such exemplification is not sufficient to satisfy the requirement set forth under 35 U.S.C. § 112, first paragraph, is further substantiated by the teachings of Peterson et al. (*Eur. J. Cancer.* 2004; **40**: 837-844). Peterson et al. teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skeptism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

In further response, despite the finding disclosed in the instant application that co-injecting mouse noggin and A549 lung cancer cells slows or reduces the formation and vascularization of tumors in immunocomprised mice, it is disturbing that contacting A549 lung cancer cell line with noggin *in vitro* promotes, rather than inhibits the growth of the cells. Why is it that mouse noggin acts to suppress the growth these cells *in vitro* but when injected into mice together with the cells apparently causes a reduction in their ability to form tumors? It is submitted that such a paradoxical finding is at odds with most, if not all other studies of potential therapeutic agents, since in general an agent that reduces the growth of tumor cells *in vitro* is expected to have the same effect *in*

vivo. The finding that noggin has *opposite* effects upon the growth of A549 lung cancer cells *in vitro* and *in vivo* would not be expected. Again, it is because of such incongruous findings that Langenfeld et al. (2003) and Langenfeld et al (2004) (both of record) suggests the need for further experimentation before concluding that BMP-2 has a role in the progression, as opposed to the suppression of cancer.

Applicant has argued the experiment described at page 58 should be considered sufficient to satisfy the requirements set forth under 35 U.S.C. § 112, first paragraph, since in Figure 10, which depicts the results of that experiment, shows the incidence of reduced tumor vascularization in mice treated with noggin, as compared to tumor vascularization in mice not so treated. This example does should not, however, be considered to serve as "working exemplification" of the claimed invention, since it merely shows reducing the growth and vascularization of lung cancer cells by co-injecting tumor cells and mouse noggin into a mouse. The claims are directed to a method for treating any tumor that overexpressed BMP-2 by reducing its vascularization by a process comprising administering to a subject a therapeutically effective amount of an inhibitor of BMP-2 activity that comprises noggin. As such the claims are directed to a method for treating *pre-established tumor in humans*. The specification does not exemplify the use of the claimed invention to reduce tumor vascularization and thereby treat the tumor, as it would be expected in its practice were it deemed enabled by its disclosure. As explained in the preceding Office action, the claimed invention cannot be practiced in the "real world" by co-injecting the polypeptide to which the claims refer (e.g., noggin) together with the tumor cells to be treated in a patient.

Langenfeld et al. (2004) (of record) discloses the results of the same or similar experiments as those described in the instant application. Although Langenfeld et al. teaches BMP-2 is overexpressed in the majority of patient-derived lung carcinomas tested, Langenfeld et al. discloses its role in cancer has not been established and while noggin appears to inhibit the growth of lung tumors in their experimental mouse model, the results of others' studies suggest inhibiting BMP-2 activity promotes tumor growth. Tada et al. (of record), for example, reports that using the same lung cancer cell line used by Langenfeld et al., the results of their studies indicate BMP-2 inhibits their

growth under anchorage-dependent and -independent growth conditions, which suggests inhibiting its activity would not be clinically beneficial, but rather detrimental to the well being of the patient diagnosed with lung cancer.

Tada et al. (of record) is not the sole disclosure of such contrary results. Buckley et al. (of record) also discloses that BMP-2 suppresses the transformed phenotype of A549 lung cancer cells. Consistently, others of record (e.g., Hardwick et al., Haramis et al., Nishanian et al., Ghosh-Choudhury et al., Tomari et al., Nakamura et al., and Wen et al.) have reported that BMP-2 has a similar role in suppressing the growth of other types of cancers, including colon cancer, breast cancer, prostate cancer, stomach cancer, and brain cancer.

Thus, just as Langenfeld et al. (2003) (of record) opines, it is apparent that the role of BMP-2 in cancer, including lung cancer has not yet been established. As a consequence, Langenfeld et al. states further studies are needed to define the role of BMP-2 in cancer.

The type and amount of exemplification disclosed are not reasonably commensurate in scope with the breadth of the claims. The claims are directed to processes comprising administering to a subject a member of a genus of inhibitors of BMP-2 activity that comprise noggin. For example, such inhibitors of BMP-2 activity comprising noggin may comprise the polypeptide of SEQ ID NO: 4 (i.e., human noggin); and yet the specification merely teaches coinjecting lung cancer cells with the polypeptide of SEQ ID NO: 2 (i.e., mouse noggin). The fact that mouse noggin may reduce the growth and vascularization of lung tumors in immunocompromised mice should not be considered a reasonable showing that an inhibitor of BMP-2 activity comprising noggin is also capable of inhibiting growth and vascularization of any other type of tumor, even if BMP-2 is overexpressed. Again, as taught by Ghosh-Choudhury et al. (of record), for example, the role of BMP-2 in other types of cancer (e.g., breast cancer) appears to be to suppress tumorigenesis; accordingly, inhibiting its activity by administering an inhibitor comprising noggin would therefore not be expected to provide therapeutic benefit. Accordingly, the skilled artisan could not use the claimed invention without undue and unreasonable experimentation.

Furthermore, the claims are not specifically limited processes for treating any one type of cancer, such as lung cancer, but rather include processes for treating any type of tumor that overexpressed BMP-2. The specification discloses that the invention is used to treat lung cancer, bladder cancer, breast cancer, colon cancer, kidney cancer, ovarian cancer, thyroid cancer, endometrial cancer, omental cancer, testicular cancer, and liver cancer; however, the specification only shows overexpression of BMP-2 in non-small cell lung cancer. Which other types of tumors can be treated using the claimed invention? Which types of tumors cannot be treated? Apart from non-small lung cell cancer, it is submitted that the disclosure does not provide sufficient guidance and direction to enable the use of the claimed invention to treat a genus of tumors that overexpress BMP-2. The skilled artisan cannot predict whether any given type of tumor overexpresses BMP-2; rather, overexpression of BMP-2 by any given type of tumor can only be empirically determined. Therefore, again, the skilled artisan could not use the claimed invention without undue and unreasonable experimentation.

Finally, it is again noted that claims 16 and 18 are specifically directed to methods comprising delivery of an expression vector encoding an inhibitor of BMP-2; as such, the claims read on treatment processes termed in the art as "gene therapy". As explained in the preceding Office action, the art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations. Applicant has not specifically addressed this issue or pointed to any disclosures in the specification, which might remedy these limitations, so as to enable the skilled artisan to use the claimed invention without undue and/or unreasonable experimentation.

In conclusion, although Applicant's arguments have been carefully considered, upon equally careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), there is a preponderance of factual evidence of record that the amount of guidance, direction, and exemplification

disclosed in the specification, as filed, would not be sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Conclusion

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
November 18, 2005